(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 July 2001 (12.07.2001)

PCT

(10) International Publication Number
WO 01/49649 A1

(51) International Patent Classification[7]: C07C 213/02, 215/54, 217/62, 49/683, 49/67, 49/223, 35/32, C07D 311/20

(21) International Application Number: PCT/SE00/02662

(22) International Filing Date:
22 December 2000 (22.12.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9904850-6 30 December 1999 (30.12.1999) SE

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(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/49649 A1

(54) Title: PROCESS OF PREPARING TOLTERODINE AND ANALOGUES THERE OF AS WELL AS INTERMEDIATES PREPARED IN THE PROCESS

(57) Abstract: The invention relates to a process for the enantioselective preparation of tolterodine and analogues and salts thereof comprising the steps of: a) enantioselectively reducing the carbonyl function in a compound of formula (II), wherein R_1, R_2, and R_3 independently of each other are hydrogen, methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen, to form an enantiomerically enriched compound of formula (IIIa) or (IIIb); b) subjecting the compound of formula (IIIa) or (IIIb) to a sigmatropic rearrangement to form a corresponding enantiomerically enriched compound of formula (IVa) or (IVb); c) subjecting the compound of formula (IVa) or (IVb) to a Baeyer-Villiger oxidation to form a corresponding enantiomerically enriched compound of formula (Va) or (Vb); d) converting the compound of formula (Va) or (Vb) to form the corresponding enantiomerically enriched compound of tolterodine or analogue thereof; and e) optionally converting a compound obtained in base form to a salt thereof, or converting a salt form to the free base. Formulas (IIIa), (IIIb), (IVa), (IVb), (Va) and (Vb) are specified in the application. The invention also relates to novel starting materials and intermediates used in the process.

PROCESS OF PREPARING TOLTERODINE AND ANALOGUES THEREOF AS WELL AS INTERMEDIATES PREPARED IN THE PROCESS

Field of the invention

The present invention relates to a novel process of preparing tolterodine and analogues thereof, as well as to novel intermediates prepared in the process.

Background of the invention

Tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, is useful for treating urinary incontinence. The major, active metabolite of tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine, contributes significantly to the therapeutic effect of tolterodine. Tolterodine and analogues thereof, including the corresponding (S)-enantiomer, as well as processes for the preparation thereof are disclosed in US-A-5,382,600. The active metabolite and analogues are disclosed in US-A-5,559,269. The (S)-enantiomer and its use in the treatment of urinary and gastrointestinal disorders is further described in WO 98/03067.

One of the processes described in US-A-5,382,600 comprises the steps of preparing the lactone 3,4-dihydro-6-methyl-4-phenyl-2H-benzopyran-2-one, reductively ring-opening the lactone to prepare the corresponding alcohol, reacting the alcohol with isopropylamine, and resolving the racemate formed to isolate tolterodine.

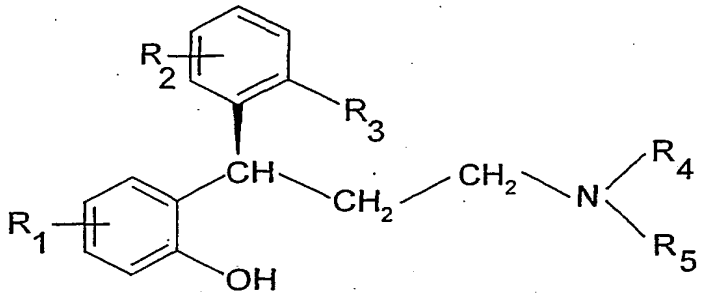
US-A-5,922,914 discloses a modified process for preparing tolterodine by reducing the above-mentioned lactone to the corresponding alcohol, 3,4-dihydro-6-methyl-4-phenyl-2H-benzopyran-2-ol, reductively aminating the alcohol, and resolving the racemate formed to isolate tolterodine.

While the above prior art methods thus produce a racemate which has to be resolved to obtain the desired tolterodine enantiomer, Andersson, Pher G. et al., J. Org. Chem. 1998, 63, 8067-8070 discloses an enantioselective synthesis of tolterodine which obviates the need of the enantiomer separation step. This method comprises a copper bromide catalyzed asymmetric addition of 2-methoxy-5-methylphenylmagnesium bromide to a 3-phenyl-prop-2-enoyl-oxazolidinone to produce the (5S)-phenyl-(3R)-(2-benzyloxy-5-methylphenyl)-3-phenylpropanoyl-2-oxazolidinone, hydrolyzation of the oxazolidinone to the corresponding propanoic acid, reaction with diisopropylamine to form the amide, and reduction of the amide to tolterodine.

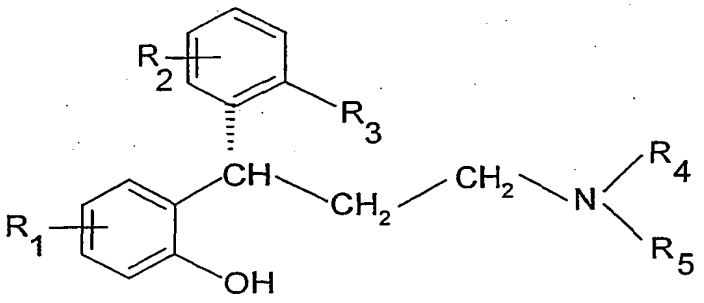
Summary of the invention

The present invention provides an alternate enantioselective synthesis of tolterodine which is more convenient to perform than the prior art method outlined above and which gives a final product of high enantiomeric purity. A key step of the present method is the preparation of the above-mentioned lactone, 3,4-dihydro-6-methyl-4-phenyl-2H-benzopyran-2-one (also referred to as 6-methyl-4-phenyl-chroman-2-one), in an enantiomerically enriched form by enantioselective reactions.

Thus, in a first aspect the present invention provides a process for the enantioselective preparation of a compound of the general formula (Ia) or (Ib):



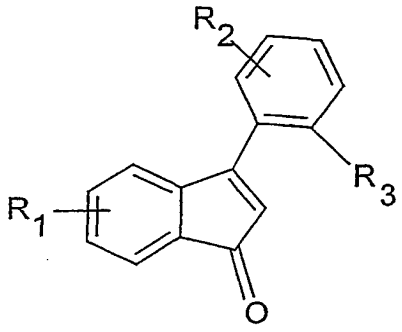
(Ia)



(Ib)

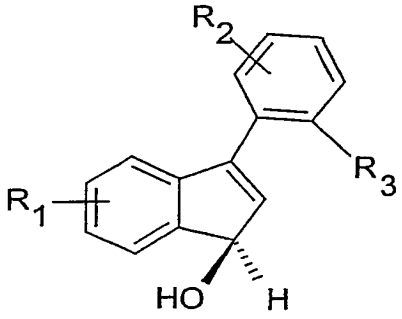
wherein R_1, R_2 and R_3 independently of each other are hydrogen, methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen, and R_4 and R_5 independently of each other are C_{1-6}-alkyl, or a salt thereof, which process comprises the steps of:

a) enantioselectively reducing the carbonyl function in a compound of formula (II):

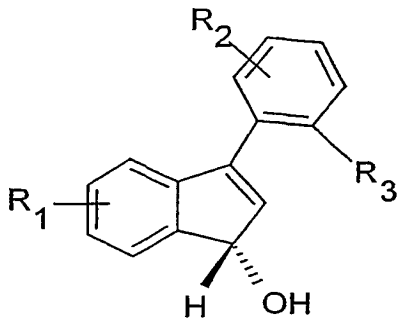


(II)

wherein R_1, R_2 and R_3 are as defined above, to form an enantiomerically enriched compound of formula (IIIa) or (IIIb):



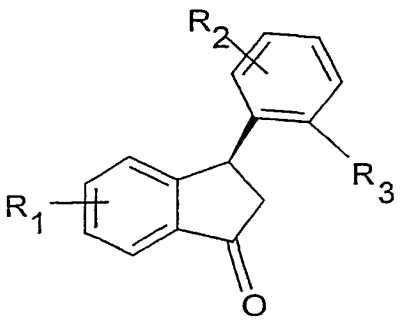
(IIIa)



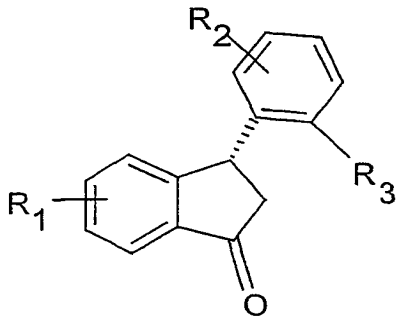
(IIIb)

wherein R_1, R_2 and R_3 are as defined above, or a salt thereof;

b) subjecting the compound of formula (IIIa) or (IIIb) to a sigmatropic rearrangement to form a corresponding enantiomerically enriched compound of formula (IVa) or (IVb):



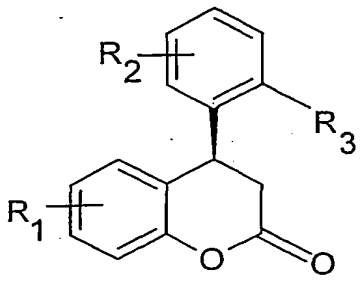
(IVa)



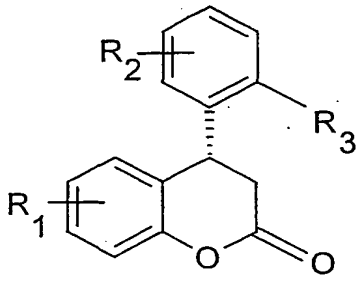
(IVb)

wherein R_1, R_2 and R_3 are as defined above, or a salt thereof;

c) subjecting the compound of formula (IVa) or (IVb) to a Baeyer-Villiger oxidation to form a corresponding enantiomerically enriched compound of the general formula (Va) or (Vb):



(Va)



(Vb)

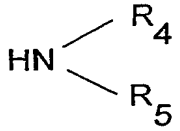
wherein R_1, R_2 and R_3 are as defined above or a salt thereof;

d) converting the compound of formula (Va) or (Vb) to form the corresponding enantiometrically enriched compound of formula (Ia) or (Ib), or a salt thereof; and

e) optionally converting a compound of formula (Ia) or (Ib) in base form to a salt thereof, or converting a salt form to the free base.

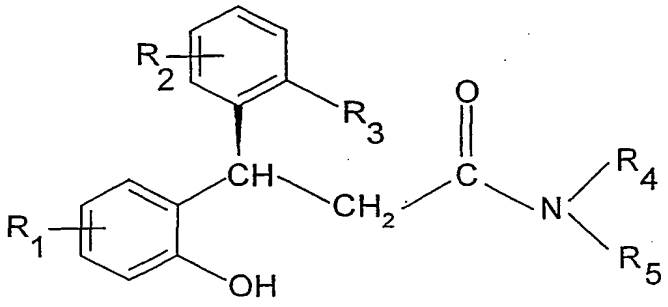
In one embodiment of the first aspect of the invention, step d) comprises:

d1) reacting the compound of formula (Va) or (Vb) with an amine of the general formula (VI):

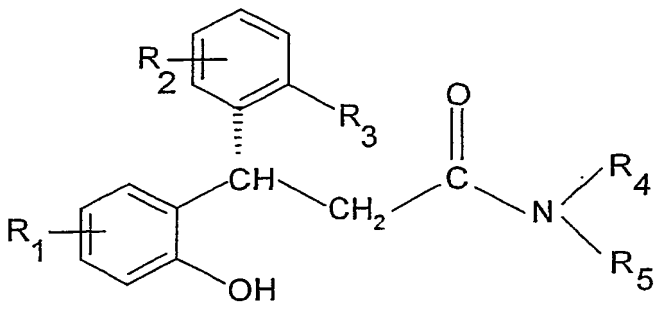


(VI)

wherein R_4 and R_5 are as defined above, to form a corresponding enantiomerically enriched compound of the general formula (VIIa) or (VIIb):



(VIIa)



(VIIb)

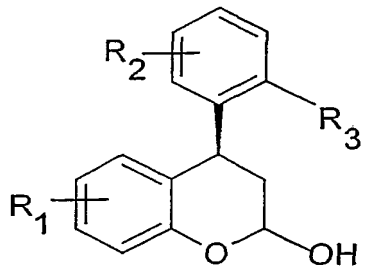
wherein R_1, R_2, R_3, R_4 and R_5 are as defined above; and

d2) reducing the carbonyl function in the compound of formula (VIIa) or (VIIb) to form the corresponding enantiomerically enriched compound of formula (Ia) or (Ib).

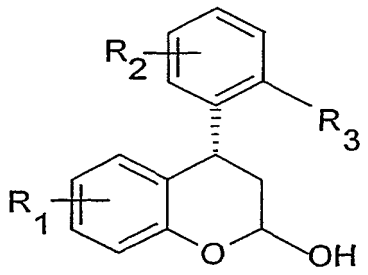
Optionally, steps d1) and d2) are performed simultaneously in a single step.

In an alternative embodiment, step d) comprises:

d1') reducing the compound of formula (Va) or (Vb) to form a corresponding enantiomerically enriched hydroxy compound of the general formula (VIIIa) or (VIIIb):



(VIIIa)

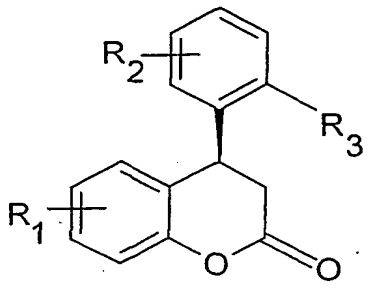


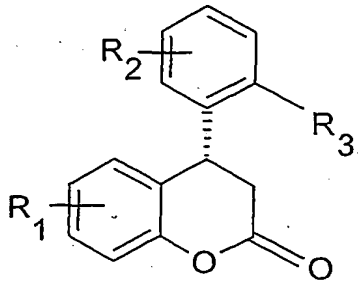
(VIIIb)

wherein R_1, R_2 and R_3 are as defined in claim 1; and

d2') reductively aminating the hydroxy compound of formula (VIIIa) or (VIIIb) with the amine of formula (VI) to form the corresponding enantiomerically enriched compound of formula (Ia) or (Ib).

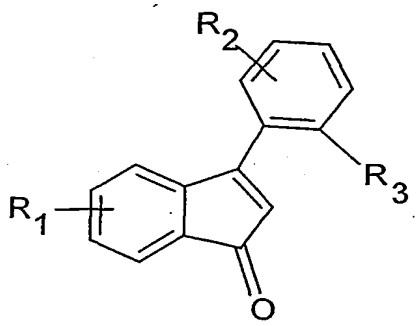
In second aspect, the present invention provides a process for the enantioselective preparation of a compound of the general formula (Va) or (Vb):


(Va)

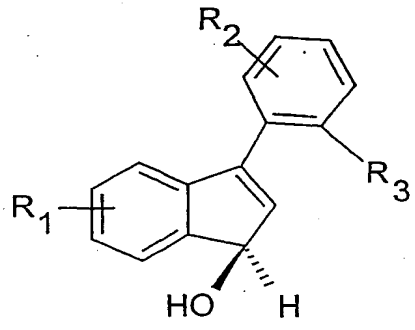

(Vb)

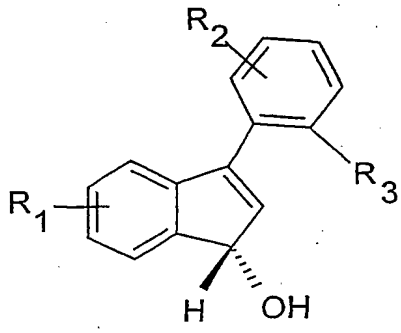
wherein R_1, R_2 and R_3 are as defined above, or a salt thereof, which process comprises the steps of:

a) enantioselectively reducing the carbonyl function in a compound of formula (II):


(II)

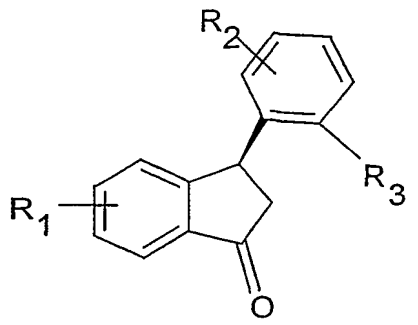
wherein R_1, R_2 and R_3 are as defined above, or a salt thereof, to form an enantiomerically enriched compound of formula (IIIa) or (IIIb):


(IIIa)

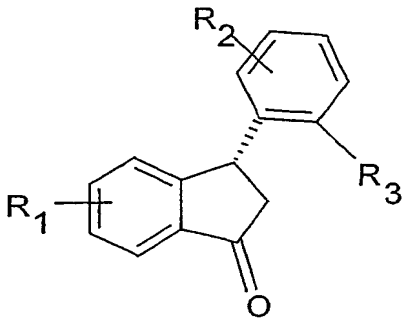

(IIIb)

wherein R_1, R_2 and R_3 are as defined above, or a salt thereof;

b) subjecting the compound of formula (IIIa) or (IIIb) to a sigmatropic rearrangement to form a corresponding enantiomerically enriched compound of formula (IVa) or (IVb):



(IVa)

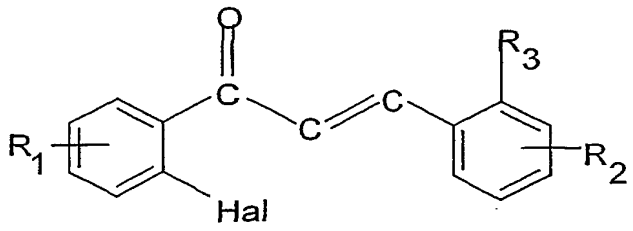


(IVb)

wherein R_1, R_2 and R_3 are as defined above, or a salt thereof; and

c) subjecting the compound of formula (IVa) or (IVb) to a Baeyer-Villiger oxidation to form the corresponding enantiomerically enriched compound of the general formula (Va) or (Vb), or salt thereof.

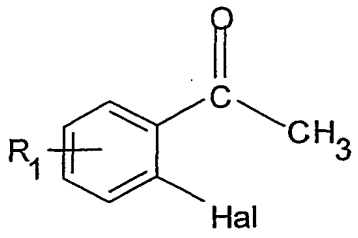
The compound of formula (II) may be prepared by subjecting a compound of the general formula (IX):



(IX)

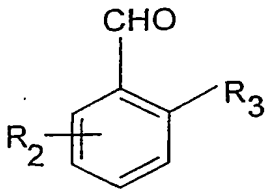
wherein R_1, R_2, and R_3 are as defined in claim 1, and Hal is halogen (preferably bromine), or a salt thereof, to a reductive ring closure reaction.

The compound of formula (IX) may be prepared by reacting a compound of the general formula (X):



(X)

wherein R_1 and Hal are as defined above, with a compound of the general formula (XI):



(XI)

wherein R_2 and R_3 are as defined above.

Preferably, compounds of formula Ia or Ib are prepared in which R_1 is methyl or hydroxymethyl in 5-position, R_2 and R_3 are hydrogen, and R_4 and R_5 are both iso-propyl.

In a third aspect, the present invention provides novel compounds of the above f of the formulae (II), (IIIa), (IIIb), (IVa), (IVb), (Va), (Vb), and (IX) as defined above and wherein R_1 is methyl or hydroxymethyl in 5-position and R_2 and R_3 are hydrogen and compounds of the formulae (IX) wherein R_1 is hydroxymethyl in 5-position, R_2 and R_3 are hydrogen and halogen is Br, J or F.

Detailed description of the invention

A basic concept behind the present invention is the enantioselective reduction of the compound of formula (II) to a compound of formula (IIIa) or (IIIb) in enantiomerically enriched form, which is then rearranged to form the lactone (Va) or (Vb). The respective lactone enantiomers may then be reacted further to tolterodine by methods known *per se* in the art, e.g. as described in the above-mentioned US-A-5,382,600 and US-A-5,922,914.

The enantioselective reduction of the compound (II) to a compound of formula (IIIa) or (IIIb) may be performed in an organic solvent with a variety of reducing agents and reaction conditions as are known *per se* in the art for enantioselective reduction of carbonyl groups. Such methods are described in, for example, Houben-Weyl, Stereoselective Synthesis, Ed: Günter Helmchen et al., Vol. 7, Chapter 2.3, Thime, Stuttgart-New York 1996. Preferably, the reaction is carried out at from about 0°C to about room temperature. An exemplary method includes the use of a chiral catalyst, such as (R)- or (S)-MeCBS (3,3-diphenyl-1-methyltetrahydro-1H,3H-pyrrolo-[1,2-c][1.3.2]oxazaborole) which is commercially available, a borane complex and a base. The stereochemistry can be directed by using either the R or S enantiomer of the MeCBS oxazaborolidine catalyst in the asymmetric borane reduction of the compound (II). The reduction of a similar substrate is described in, for example, WO 97/17341. The enantioselectivity of asymmetric borane reductions is not very sensitive to stereoelectronic effects.

The sigmatropic 1,3-rearrangement (hydride shift) of the compound (IIIa) or (IIIb) to a compound of formula (IVa) or (IVb) may be carried out by treatment with a base, such as triethylamine, and a palladium catalyst, such as Pd(dppe)Cl_2 ([1,2-bis(diphenylphosphino)ethane]palladium (II) chloride) in an organic solvent (see e.g. the above WO 97/17341). Alternatively, the rearrangement reaction may be carried out by treatment with DABCO (1,4-diazabicyclo[2.2.2]octane) and a base, such as triethylamine, in an organic solvent (see Example 1 below). The indanone (IVa) or (IVb) obtained is generally a highly crystalline solid which makes it possible to raise the enantiomeric purity, if desired, by recrystallization from a suitable solvent (for example, an enantiomeric excess (as defined below) of 99% or more may be obtained).

The Baeyer-Villiger oxidation of compounds (IVa) and (IVb) may be performed by a variety of oxidizing agents as is well known in the art, e.g. hydrogen peroxide or a peroxy acid, such as 3-chloro-peroxybenzoic acid, preferably in the presence of an acid catalyst, such as p-tolylsulphonic acid (TsOH). The reaction is preferably carried out in an organic solvent and at e.g. from about 0°C to about room temperature.

Enantiomeric purity, or enantiomeric enrichment, is usually expressed as "enantiomeric excess", below abbreviated as "ee", and defined as (R-S)/(R+S), where R and S are the amounts of the R- and S-enantiomers, respectively. For the purposes of the

present invention, the enantiomeric purity in the enantioselective process steps is usually at least about 50%, preferably at least about 85%.

Since tolterodine is an amine, it may form salts with both organic and inorganic acids. The pharmaceutically acceptable salts may, depending on the pharmaceutical formulation, be preferred over the corresponding free amines since they produce compounds which are more water soluble and more crystalline. Exemplary pharmaceutically acceptable salts include salts with acids such as methane sulphonic, hydrochloric, hydrobromic, sulphuric, phosphoric, nitric, benzoic, citric, tartaric, fumaric, and maleic acids.

The invention will now be illustrated further by the following non-limiting Example.

In the Example:

TLC refers to thin-layer chromatography.

MeCBS refers to 3,3-diphenyl-1-methyltetrahydro-1H,3H-pyrrolo-[1,2-c][1.3.2]oxazaborole.

DABCO refers to 1,4-diazabicyclo[2.2.2]octane.

ChiralCel OD-H (trademark) refers to a chiral stationary phase for liquid chromatography consisting of cellulose tris(3,5-dimethylphenyl carbamate) on a silica gel substrate (Daicel Chemical Industries, Ltd).

mCPBA refers to 3-chloroperoxybenzoic acid.

"ee" refers to enantiomeric excess as defined above.

EXAMPLE 1:

1-(2-Bromo-4-methyl-phenyl)-3-phenyl-propenone

To a solution of 2-bromo-4-methylacetophenone (7.20 g, 34.0 mmol) and benzaldehyde (3.65 g, 34.0 mmol) in dry methanol (50 ml) was added freshly prepared sodium methoxide (35.7 mmol) in dry methanol (30 ml) at 0°C. The resulting mixture was stirred at 0°C for 5 h and raised to room temperature over night. 10 ml of HCl (10%) were added slowly and the mixture was evaporated to near dryness under reduced pressure. The residue was suspended in saturated $NaHCO_3$ (50 ml) and extracted with 3x50 ml diethyl ether, washed with brine and dried over $MgSO_4$. Purification by flash chromatography eluting with diethyl ether:pentane 5:95, gave 10.1

g (95%) of the title compound. R_f 0.66 (diethyl ether: pentane 20:80). ^{1}H NMR δ: 2.25 (s, 3H), 6.06 (d, J= 10.2Hz, 1H), 7.15 (d, J= 10.2Hz, 1H), 7.05 (dd, J= 7.6Hz, 2.6Hz, 1H), 7.24 (m, 3H), 7.34 (m, 2H), 7.40 (m, 3H). ^{13}C NMR δ: 21.4, 112.5, 117.3, 122.5, 122.8, 123.7, 124.9, 128.4, 132.2, 133.6, 133.9, 143.6, 145.3, 186.6.

5-Methyl-3-phenyl-inden-1-one

To a suspension of anhydrous K_2CO_3 (9.76 g, 70.6 mmol) in dry DMF (100 ml) was added 1-(2-bromo-4-methyl-phenyl)-3-phenyl-propenone (8.40 g, 28.3 mmol), and the mixture was deaerated with dry argon for 15 min. Triphenylphosphine (0.73 g, 2.83 mmol) was added followed by $PdCl_2$ (0.20 g, 1.13 mmol). The mixture was heated at 80°C until NMR sample indicated disappearance of starting material (5 h). The mixture was reduced to half volume under reduced pressure and poured on ice:water (200 ml). Extractive work-up with CH_2Cl_2 followed by flash chromatography eluting with diethyl ether:pentane 5:95 gave 4.2 g (72%) of the title compound. R_f 0.62 (diethyl ether: pentane 20:80). IR (neat cm^{-1}): 1704, 1606, 1355, 1101, 815, 743. ^{1}H NMR δ: 2.40 (s, 3H), 5.99 (s, 1H), 7.11 (d, J= 7.2Hz, 1H), 7.18 (s, 1H), 7.43 (d, J= 7.6Hz, 1H), 7.53 (m, 3H), 7.66 (m, 2H). ^{13}C NMR δ: 22.1, 122.7, 122.9, 123.5, 127.4, 128.6, 128.9, 129.2, 129.9, 130.3, 133.2, 143.7, 144.4, 162.4. MS (EI 70 eV) *m/z* (rel. intensity): 220 (100) [M$^+$], 205 (75), 191 (51), 177 (10), 165 (15).

5-Methyl-3-phenyl-(S)-1H-inden-1-ol

(R)-MeCBS catalyst (0.22 ml, 1 M, 0.22 mmol) was mixed in 5 ml of dry THF, and stirred for 1 h at room temperature. After cooling to 0°C, 2.5 ml of 2 M BH_3:Me_2S (4.99 mmol) in THF were added. 5-Methyl-3-phenyl-inden-1-one (1.00 g, 4.54 mmol) was added as a solution in toulene (2 ml) over 2 h via a syringe pump. The reaction was followed by TLC. After completeness, methanol (0.6 ml, 17 mmol) was added at 0°C and the mixture was evaporated to dryness. Flash chromatography eluting with ethyl acetate:pentane 10:90 gave 0.96 g (95%) of the title compound. R_f 0.35 (ethyl acetate:pentane 20:80) (ChiralCel OD-H) 0.5 ml/min of hexane/isopropanol: 95/5 (*S*)-isomer 24.53 min, (*R*)-isomer 27.22 min, 93% ee. IR (neat cm^{-1}): 3300, 1605, 1446, 949, 813. ^{1}H NMR δ: 1.40 (s, 1H), 2.40 (s, 3H), 5.27 (d, J= 8Hz, 1H), 6.43 (d J= 2Hz, 1H), 7.18 (d, J= 8Hz, 1H), 7.27 (s, 1H), 7.47 (m, 4H), 7.59 (m, 2H). ^{13}C NMR δ: 21.6, 76.2, 121.6, 123.6, 126.9, 127.6, 128.2, 128.6, 134.1, 134.9, 138.2, 142.1, 143.7, 145.6.

MS (EI 70eV) *m/z* (rel. intensity): 220 (100) [M^+], 207 (71), 178 (66), 144 (42), 116 (23).

5-Methyl-3-(S)-phenyl-indan-1-one

5-Methyl-3-phenyl-(S)-1H-inden-1-ol (750 mg, 3.41 mmol) and DABCO (190 mg, 1.71 mmol) were dissolved in dry THF:triethylamine 20:1 (15 ml) and refluxed for 3 h. The reaction mixture was evaporated to dryness. Flash chromatography eluting with ethyl acetate:pentane 5:95 gave 690 mg (92%) of the title compound. R_f 0.62 (ethyl actetate:pentane 20:80) (ChiralCel OD-H) 0.5 ml/min of hexane/isopropanol: 95/5 (*S*)-isomer 19.12 min, (*R*)-isomer 22.33 min, 89% ee. IR (neat cm^{-1}): 3027, 2361, 1710, 1605, 1280, 1238, 1040. ^1H NMR δ: 2.39 (s, 3H), 2.69 (dd, $J = 3.0$, 19.2Hz, 1H), 3.23 (dd, $J = 8.0$, 19.2Hz, 1H), 4.53 (q, $J = 4$Hz, 1H), 7.07 (s, 1H), 7.14 (d, $J = 8.4$Hz, 1H), 7.15 (s, 1H), 7.26 (m, 2H), 7.33 (m, 2H), 7.72 (d, $J = 7.6$Hz, 1H). ^{13}C NMR δ: 22.1, 44.3, 46.9, 123.2, 126.9, 127.0, 127.6, 128.9, 134.5, 143.8, 146.3, 158.4, 205.5. MS (EI 70 eV) *m/z* (rel. intensity): 220 (100) [M^+], 207 (55), 194 (19), 178 (60), 144 (10).

6-Methyl-4-(S)-phenyl-chroman-2-one

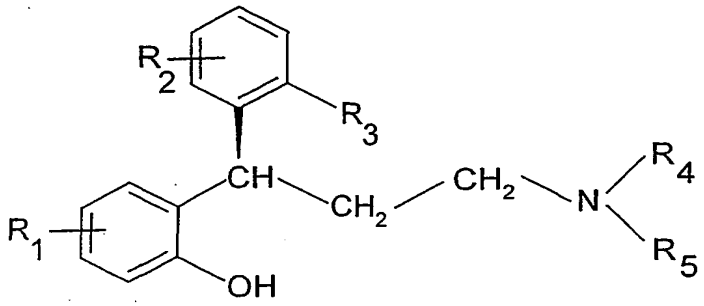
5-Methyl-3-(S)-phenyl-indan-1-one (400 mg, 1.8 mmol) and *m*CPBA (98%, 485 mg, 2.8 mmol) were suspended in dry CH_2Cl_2 (6 ml) at 0°C followed by TsOH:H_2O (20 mg). The reaction was kept at 4°C for 48 h. The mixture was diluted with 10 ml of CH_2Cl_2 and washed with 2x10 ml of saturated Na_2SO_3, saturated $NaHCO_3$ and brine. Flash chromatography eluting with ethyl acetate:pentane 10:90 gave 390 mg (90%) of the title compound. R_f 0.83 (ethyl acetate:pentane 20:80) (ChiralCel OD-H) 0.5 mL/min of hexane/isopropanol 95/5 (*S*)-isomer 15.18 min, (*R*)-isomer 17.42 min, 89% ee. IR (neat cm^{-1}): 2900, 2360, 1769, 1495, 1208, 1145. ^1H NMR δ: 2.28 (s, 3H), 3.05 (m, 1H), 4.32 (t, $J = 6.8$Hz, 1H), 6.98 (s, 1H), 7.04 (d, $J = 8.4$Hz, 1H), 7.11 (dd, $J = 2.0$, 8.4Hz, 1H), 7.18 (d, $J = 8.4$Hz, 1H), 7.19 (s, 1H), 7.33 (m, 3H) ^{13}C NMR δ: 20.7, 37.1, 40.7, 116.8, 125.3, 127.5, 127.6, 128.6, 129.1, 129.3, 134.3, 140.5, 149.6, 167.8. MS (EI 70 eV) *m/z* (rel. intensity): 238 (55) [M^+], 220 (57), 195 (100), 181(10), 165 (12), 152 (9).

(R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine (tolterodine)

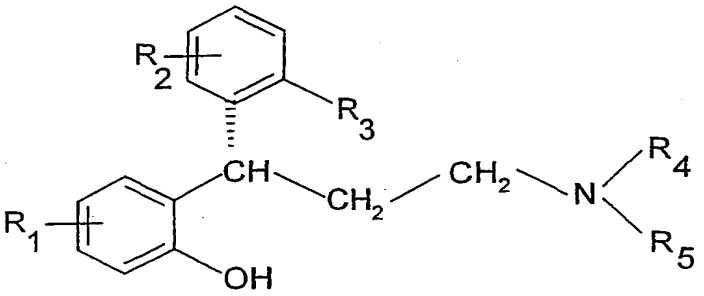
Tolterodine may be prepared from 6-methyl-4-(S)-phenyl-chroman-2-one as obtained above by method steps corresponding to Examples 3 and 4 of the above-mentioned US 5,922,914 (the full disclosure of which is incorporated by reference herein), i.e. by (i) reducing the lactone 6-methyl-4-(S)-phenyl-chroman-2-one with diisobutylaluminiumhydride in toluene solution at –20 to -25°C to the corresponding hydroxy compound, 6-methyl-4-(S)-phenyl-chroman-2-ol; (ii) reductively aminating the 6-methyl-4-(S)-phenyl-chroman-2-ol in methanol by reaction with diisopropylamine and hydrogenation with palladium on carbon at 45-50 psi and 48°C, and subsequent filtration (solka floc) to obtain the title compound (tolterodine) in substantially enantiomerically pure form.

CLAIMS

1. A process for the enantioselective preparation of a compound of the general formula (Ia) or (Ib):



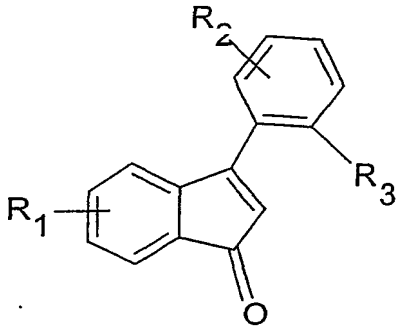
(Ia)



(Ib)

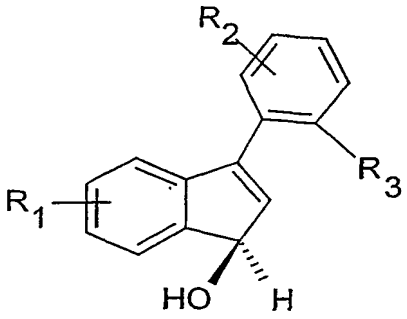
wherein R_1, R_2 and R_3 independently of each other are hydrogen, methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen, and R_4 and R_5 independently of each other are C_{1-6}-alkyl, or a salt thereof, which process comprises the steps of:

a) enantioselectively reducing the carbonyl function in a compound of formula (II):

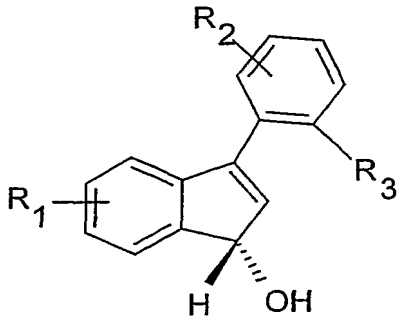


(II)

wherein R_1, R_2 and R_3 are as defined above, to form an enantiomerically enriched compound of formula (IIIa) or (IIIb):



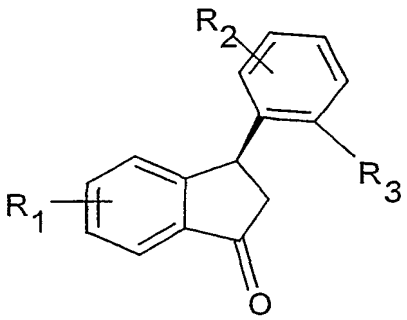
(IIIa)



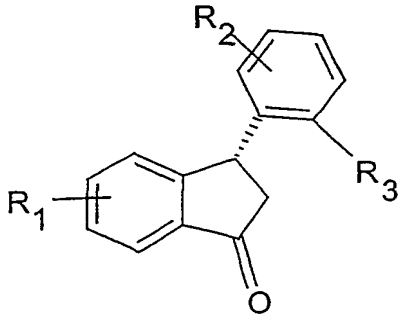
(IIIb)

wherein R_1, R_2 and R_3 are as defined above;

b) subjecting the compound of formula (IIIa) or (IIIb) to a sigmatropic rearrangement to form a corresponding enantiomerically enriched compound of formula (IVa) or (IVb):



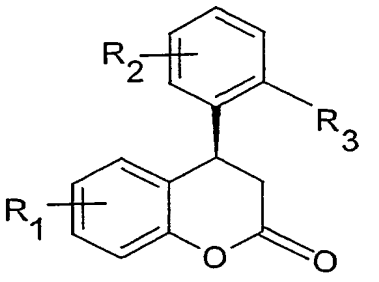
(IVa)



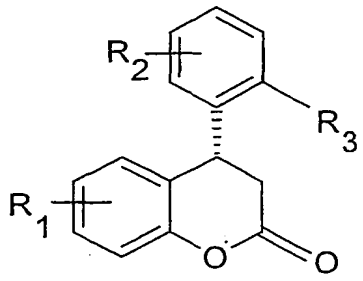
(IVb)

wherein R_1, R_2 and R_3 are as defined above;

c) subjecting the compound of formula (IVa) or (IVb) to a Baeyer-Villiger oxidation to form a corresponding enantiomerically enriched compound of the general formula (Va) or (Vb):



(Va)



(Vb)

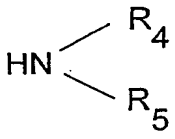
wherein R_1, R_2 and R_3 are as defined above;

d) converting the compound of formula (Va) or (Vb) to form the corresponding enantiometrically enriched compound of formula (Ia) or (Ib); and

e) optionally converting the compound of formula (Ia) or (Ib) to a salt thereof.

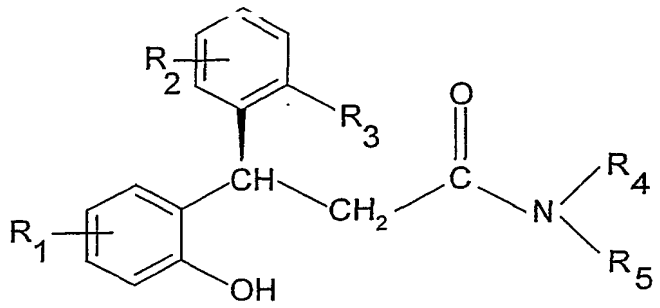
2. The process according to claim 1, wherein step d) comprises:

d1) reacting the compound of formula (Va) or (Vb) with an amine of the general formula (VI):

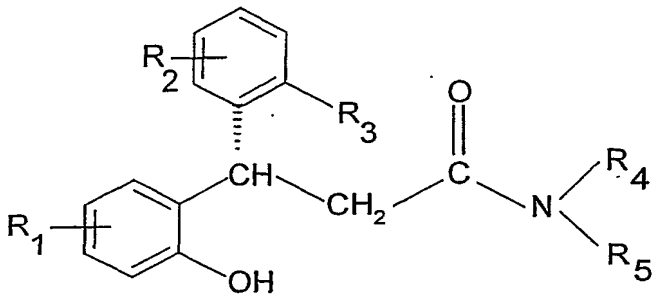


(VI)

wherein R_4 and R_5 are as defined in claim 1, to form a corresponding enantiomerically enriched compound of the general formula (VIIa) or (VIIb):



(VIIa)



(VIIb)

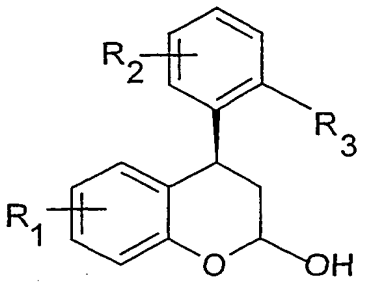
wherein R_1, R_2, R_3, R_4 and R_5 are as defined above; and

d2) reducing the carbonyl function in the compound of formula (VIIa) or (VIIb) to form the corresponding enantiomerically enriched compound of formula (Ia) or (Ib).

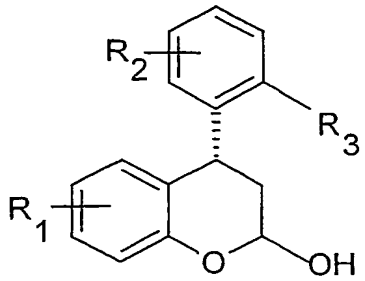
3. The process according to claim 2, wherein steps d1) and d2) are performed simultaneously in a single step.

4. The process according to claim 1, wherein step d) comprises:

d1') reducing the compound of formula (Va) or (Vb) to form a corresponding enantiomerically enriched hydroxy compound of the general formula (VIIIa) or (VIIIb):



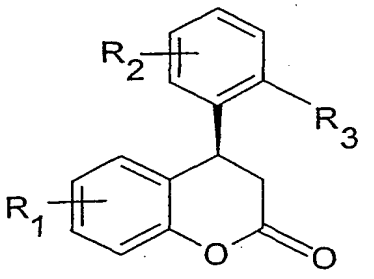
(VIIIa)



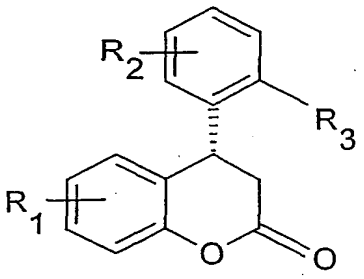
wherein R_1, R_2 and R_3 are as defined in claim 1; and

d2') reductively aminating the hydroxy compound of formula (VIIIa) or (VIIIb) with the amine of formula (VI) to form the corresponding enantiomerically enriched compound of formula (Ia) or (Ib).

5. A process for the enantioselective preparation of a compound of the general formula (Va) or (Vb):



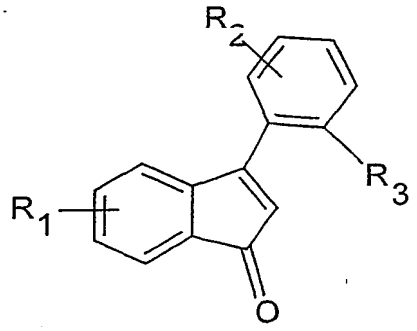
(Va)



(Vb)

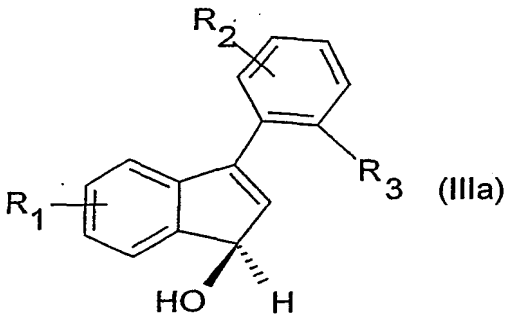
wherein R_1, R_2 and R_3 are as defined in claim 1, or a salt thereof, which process comprises the steps of:

a) enantioselectively reducing the carbonyl function in a compound of formula (II):

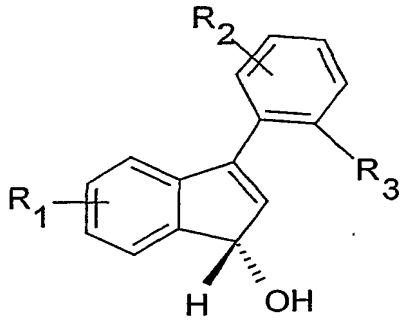


(II)

wherein R_1, R_2 and R_3 are as defined above, or a salt thereof, to form an enantiomerically enriched compound of formula (IIIa) or (IIIb):



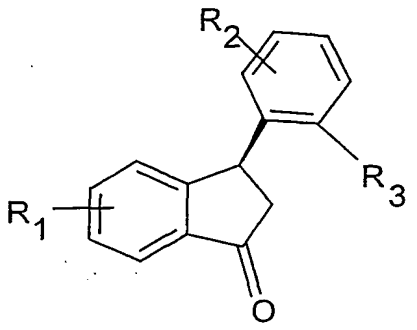
(IIIa)



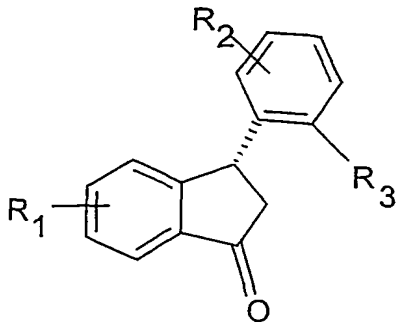
(IIIb)

wherein R_1, R_2 and R_3 are as defined above, or a salt thereof;

b) subjecting the compound of formula (IIIa) or (IIIb) to a sigmatropic rearrangement to form a corresponding enantiomerically enriched compound of formula (IVa) or (IVb):



(IVa)

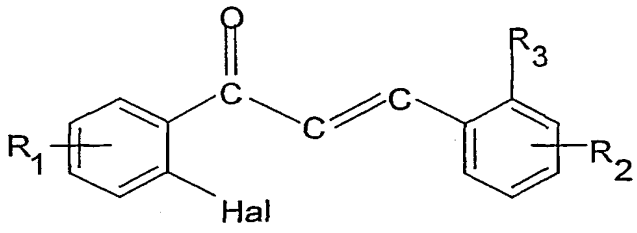


(IVb)

wherein R_1, R_2 and R_3 are as defined above, or a salt thereof; and

c) subjecting the compound of formula (IVa) or (IVb) to a Baeyer-Villiger oxidation to form the corresponding enantiomerically enriched compound of the general formula (Va) or (Vb), or salt thereof.

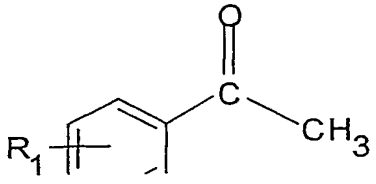
6. The process according to any one of claims 1 to 5, which further comprises preparing the compound of formula (II) by subjecting a compound of the general formula (IX):



(IX)

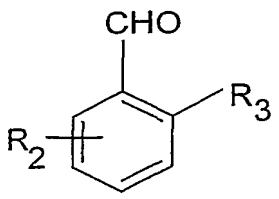
wherein R_1, R_2, and R_3 are as defined in claim 1, and Hal is halogen, or a salt thereof, to a reductive ring closure reaction.

7. The process according to claim 6, further comprising preparing the compound of formula (IX) by reacting a compound of the general formula (X):



(X)

wherein R_1 and Hal are as defined above, with a compound of the general formula (XI):



(XI)

wherein R_2 and R_3 are as defined in claim 1.

8. The process according to any one of claims 1 to 7, wherein R_1 is methyl or hydroxymethyl in 5-position, R_2 and R_3 are hydrogen, and R_4 and R_5 are both iso-propyl.

9. The process according to any one of claims 1 to 4 and 6 to 8, wherein tolterodine is prepared.

10. Compounds of the formulae (II), (IIIa), (IIIb), (IVa), (IVb), (Va) and (Vb) as defined in claims 1 to 8 and wherein R_1 is methyl or hydroxymethyl in 5-position and R_2 and R_3 are hydrogen and compounds of the formulae (IX) wherein R_1 is hydroxymethyl in 5-position, R_2 and R_3 are hydrogen and halogen is Br, J or F.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02662

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07C 213/02, C07C 215/54, C07C 217/62, C07C 49/683, C07C 49/67, C07C 49/223, C07C 35/32, C07D 311/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07C, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Organic Letters, Volume 1, No 11, 1999, William M. et al, "A Highly Enantioselective Conjugate Reduction of 3-Arylinden-1-ones Using Bakers´ Yeast for the Preparation of (S)-3-Arylindan-1-ones.", page 1839 - page 1842, see page 1840, scheme 4 and page 1841, scheme 5 --	6,10
A	WO 9717330 A1 (SMITHKLINE BEECHAM CORPORATION), 15 May 1997 (15.05.97), see page 44, line 8 --	10
A	Tetrahedron Letters, Volume 23, 1976, A. I. Meyers et al, "An Asymmetric Synthesis of 5-methoxy-3-substituted Acids and Their Related Lactones in High Enantiomeric Purity", page 1947 - page 1950, see page 1949, compound 15 --	10

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 April 2001	06 -04- 2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Nebil Gecer/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02662

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J. Org. Chem., Volume 63, 1998, Pher G. Andersson et al, "Assymmetric Total Synthesis of (+)-Tolterodine, a New Muscarinic Receptor Antagonist, via Copper-Assisted Asymmetric Conjugate Addition of Aryl Grignard Reagents to 3-Phenyl-prop-2-enoyl-oxazolidinones" page 8067 - page 8070	1-5,8-9,10
A	WO 9829402 A1 (PHARMACIA & UPJOHN COMPANY), 9 July 1998 (09.07.98)	1-5,8-9,10
A	WO 8906644 A1 (KABIVITRUM AB), 27 July 1989 (27.07.89)	1-5,8-9,10
A	J. Med. Chem., Volume 41, 1998, Simon Feldbaek Nielsen et al, "Antileishmanial Chalcones: Statistical Design, Synthesis, and Three-Dimensional Quantitative Structure-Activity Relationship Analysis", page 4819 - page 4832, see e.g. page 4820, table 3 and page 4826	7,10
A	J. Med. Chem., Volume 36, 1993, Douglas G. Batt et al, "2-Substituted Chalcone Derivatives as Inhibitors of Interleukin-1 Biosynthesis", page 1434 - page 1442, see page 1435, scheme I, method A and page 1436, table II.	7,10
A	J. Med. Chem., Volume 36, 1993, Satoshi Sogawa et al, "3,4-Dihydroxychalcones as Potent 5-Lipoxygenase and Cyclooxygenase inhibitors", page 3904 - page 3909, see page 3904, right-hand column, second paragraph and page 3906, table II	7,10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02662

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J. Indian. Chem. Soc., Volume LXV, 1988, Krishna C. Joshi et al, "Facile Synthesis of Fluorine containing 1,3,5-Triarylpyrazoles and 3, 5-Diarylisoxazoles" page 773 - page 777 --	7,10
A	STN International, file CAPLUS, CAPLUS accession no. 1970:31393, Hsu, K.K. et al, "Synthesis of sulfamylchalcones" J. Chin. Chem. Soc. (Taipei) (1969), 16(3), 91-6 --	7,10

Form PCT/ISA/210 (continuation of second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

In...tional application No.
PCT/SE00/02662

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

see next sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

According to PCT Rules 13.1 and 13.2, an international application shall relate to one invention only or a group of inventions linked by one or more of the same corresponding "special technical features", i.e. features that define a contribution which each of the inventions makes over the prior art.

In the present application the following inventions have been found:

Invention 1 according to claims 1-5, 8-9, 10 (those parts relating to the compounds II, IIIa, IIIb, IVa, IVb, Va, Vb):
relates to a process for the enantioselective preparation of tolterodine or analogs thereof (formula Ia and Ib). Furthermore, invention I relates to the intermediates II, IIIa, IIIb, IVa, IVb, Va, Vb and to a process for the preparation of Va and Vb. The mentioned intermediates and the final products Ia and Ib are linked by a common structural feature.

Invention 2 according to claims 6-7, 10 (those parts relating to the compound IX):
relates to a process for the preparation of the intermediate II from IX and to a process for the preparation of IX. Furthermore, invention 2 relates to IX. The compound IX differs structurally from both the final products Ia and Ib as well as the other intermediates.

Inventions 1 and 2 are not linked by any common special technical feature. Thus, the inventions lack unity.

INTERNATIONAL SEARCH REPORT

Information on patent family members

25/02/01

International application No.
PCT/SE 00/02662

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